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C07K 16/00

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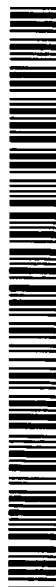
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For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: HUMAN INFLAMMATORY BREAST CARCINOMA XENOGRAFT CAPABLE OF LYMPHOVASCULAR INVA-  
SION AND METHODS FOR ITS USE

(57) Abstract: The present invention provides human transplantable inflammatory breast carcinoma xenografts. Such xenografts exhibit a number of unique characteristics which allows their use in experimental models of inflammatory carcinoma in order to dissect out the molecular basis of this phenotype. This experimental model of inflammatory carcinoma can be used to identify molecular targets for therapeutic intervention and to assess the efficacy of a broad spectrum of diagnostic and therapeutic agents. Specific animal models of inflammatory breast cancer are described as well as methods for evaluating diagnostic and therapeutic agents for treating inflammatory breast cancer. Methods for identifying molecules whose expression is modulated in inflammatory breast cancer are provided. In addition, methods for diagnosing and inhibiting the growth of inflammatory breast cancer metastases in vivo are provided.



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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/25299

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : Please See Extra Sheet.

US CL : 424/152.1; 435 7.1, 29, 366, 371; 53 /387.1; 800/3, 10

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/152.1; 435 7.1, 29, 366, 371; 530/387.1; 800/3, 10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST, Biosis, CAPLUS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|-----------|--|-----------------------|
| A         | CHRYSOGELOS, S.A. Chromatin Structure of the EGRF Gene Suggests a Role for Intron 1 Sequences in its Regulation in Breast Cancer Cells. Nucleic Acids Research. 1993, Vol. 21, No. 24, pages 5736-5741.                | 1-9                   |
| A         | SCHIEMANN, S. et al. Molecular Analysis of Two Mammary Carcinoma Cell Lines at the Transcriptional Level as a Model System for Progression of Breast Cancer. Clinical Experimental Metastasis. 1998, Vol. 16, 129-139. | 1-9                   |

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

|   |  |
|---|--|
| * Special categories of cited documents:  | "T" Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  |
| "A" document defining the general state of the art which is not considered to be of particular relevance  | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone   |
| "E" earlier document published on or after the international filing date  | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "G" document member of the same patent family  |
| "O" document referring to an oral disclosure, use, exhibition or other means  |  |
| "P" document published prior to the international filing date but later than the priority date claimed  |  |

Date of the actual completion of the international search

24 NOVEMBER 2000

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**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/US00/25299

**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|-----------|--|-----------------------|
| A         | BRUNNER, N. et al. Effect of Endocrine Therapy on Growth of T61 Human Breast Cancer Xenografts is Directly Correlated to a Specific Down-Regulation of Insulin-Like Growth Factor II (IGF-II). European Journal of Cancer. 1993, Vol. 29A, No. 4, 562-569. | 1-9                   |
| A         | GUERIN, M. et al. Structure and Expression of c-erbB-2 and EGF Receptor Genes in Inflammatory and Non-Inflammatory Breast Cancer. Prognostic Significance. International Journal of Cancer. 1989, Vol. 43, pages 201-208.                                  | 1-9                   |
| X         | SHAO, M. et al. A Human Inflammatory Breast Carcinoma Xenograft Model of the Intravasation Step of Metastasis. FASEB Journal. 12 March 1999, Vol. 13, No. 4 PART 1, page A187, abstract No. 174.9, see entire abstract.                                    | 1-9                   |
| A         | CHUN, M. Plasmin Induces the Formation of Multicellular Spheroids of Breast Cancer Cells. Cancer Letters. 1997, Vol. 117, pages 51-56.   | 1-9                   |
| Y         | US 5,508,188 A (BARKSKY et al) 16 April 1996, col. 1, lines 20-44, col. 11, line 35 to col. 12, lines 39 and col. 13, lines 25-55.   | 1-9                   |

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## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-9, drawn to a human inflammatory breast cancer xenograft and a method of generating a human inflammatory breast cancer xenograft.

Group II, claim(s) 10-12, drawn to a non-human animal model for inflammatory breast cancer.

Group III, claim(s) 13-18, drawn to a method for evaluating treatments of inflammatory breast cancer.

Group IV, claim(s) 19-22, drawn to a method for evaluating at least one agent for identifying inflammatory breast cancer.

Group V, claim(s) 23-27, drawn to a method for evaluating the potential of an agent for the prevent of lymphovascular invasion of cancer cells.

Group VI, claim(s) 28 and 29, drawn to a method for identifying a molecule whose expression is modulated in inflammatory breast cancer.

Group VII, claim(s) 30, 36-41 and 43-47, drawn to a method of inhibiting the growth of inflammatory breast cancer metastasis.

Group VIII, claim(s) 31 and 36-41 drawn to a method of detecting an inflammatory breast cancer metastasis.

Group IX, claim(s) 32 and 33, drawn to a conjugate of an anti-E-cadherin antibody jointed to a cytotoxic agent.

Group X, claim(s) 34 and 35, drawn to an E-cadherin antibody labeled with a detectable marker.

Group XI, claim(s) 42, drawn to a recombinant antibody with human constant regions and murine antigen binding regions.

Group XII, claim(s) 48 and 49, drawn to a kit or an article of manufacture comprising an E-cadherin specific polypeptide comprising an antigen binding site of an E-cadherin antibody.

The inventions listed as Groups I-II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The claims lack a special technical feature as xenografts of human cancer cells, their growth in immunocompromised non-human animals, and the use of the animals as models for testing therapeutics was known in the art at the time of filing. U.S. Patent 5,508,188 issued 06 April 1996 teaches the establishment of a human cancer xenograft in nude mice and the use of the mouse as a model for testing various agents for effectiveness against the cancer (col. 13, lines 25 to col. 14, lines 54). Further, PCT rules do not permit for multiple separate products and methods to be examined together (37 CFR 1.475 (b) and (d)).

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/25299

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8

Remark on Protest

☐  
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.